

Seroepidemiological Study of Measles After the 1992 Nationwide MMR Revaccination Program in Taiwan

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The incidence of measles declined rapidly in Taiwan after the introduction of the measles vaccine into the routine immunization schedule in 1978. However, an epidemic still occurred every 3–5 years until recently. A nationwide measles-mumps-rubella (MMR) revaccination program for school and preschool children has been in place since 1992 to control the indigenous transmission of measles. In order to understand the current immune status after this recent nationwide revaccination program, we determined the presence of measles IgG antibodies by enzyme-linked immunosorbent assay (ELISA) in 1,281 blood samples from healthy persons aged from 2 months to above 30 years collected between 1993 and 1995, and also in another batch of 90 sera samples from children aged 2 years collected before 1992. The results showed that 1) the measles antibody seropositive rate (36.4%) was lowest in children aged 5–7 months and rose to an unexpectedly high level of 85.8% at the age of 12–14 months, 2) the seropositive rate rose further to between 85.9% and 95.1% after 2 years of age and remained high in adults and pregnant women, and 3) the seropositive rate of the 2-year-old children collected before 1992 was 61.4%, which was significantly lower than the rate of the same age group collected after the nationwide MMR revaccination program. We conclude that the national revaccination program has promoted effectively measles immunity in Taiwan. This immunity explains the rarity of reported measles cases since the last epidemic in 1989. This revaccination program should continue and be extended to all preschool children and young adults so that indigenous measles can be eliminated by the year 2000. *J Med Virol* 51:32–35, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: immunization; maternal antibodies; measles

INTRODUCTION

Measles is a highly contagious disease with significant morbidity and mortality. Currently, measles control relies mainly on active immunization with a live, attenuated vaccine. Previous studies suggested that we may eliminate measles from a population by high vaccination coverage [Krugman et al., 1963; Baba et al., 1984]. However, it has been noted recently that measles epidemics can occur even in a fully immunized population [Gustafson et al., 1987; Davis et al., 1987; Chen et al., 1989]. Regular use of measles vaccine has reduced dramatically the incidence of measles. Although more than 50% of counties in the United States had remained free of measles for a decade or more, two main patterns of measles transmission continued. First, outbreaks continued to occur among highly vaccinated school-age populations, in which measles transmission was documented among children who had received a single dose of vaccine [Gustafson et al., 1987]. The second pattern, as observed in the large epidemics of 1988–1991, was transmission within unvaccinated ethnic and racial minority preschool children, particularly in the inner cities [Hersh et al., 1992]. A booster dose of MMR vaccine before attending primary school or at 10–12 years old is currently suggested in the United States. This booster is intended to increase overall vaccine coverage and to reduce primary and secondary vaccine failures.

In the prevaccination era, measles was an inevitable disease before reaching adulthood [Chen et al., 1984], and there would be large-scale measles outbreaks every 2 years in Taiwan. Measles vaccine was introduced to Taiwan in 1968. A mass immunization program with one dose of vaccine for 9 to 36-month-old children was instituted in Taipei city in 1977, and later for children aged 15–21 months throughout Taiwan in 1978. The policy reduced effectively measles mortality with only one fatal case reported in 1983 [Department of Health,

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1986]. However, measles outbreaks continued to occur every 3–5 years [Hsu, 1987; Lee et al., 1987, 1992]. Two recent measles outbreaks in Taiwan affected 2,219 patients in 1985 and 2,446 subjects in 1988–1989 [Lee et al., 1987, 1992]. Detailed analysis of these outbreaks found that most victims were unvaccinated and one fourth of them were infants. To combat measles, the Advisory Committee of Immunization Practice (ACIP) in Taiwan decided in May 1988 to change the previous one-dose measles immunization schedule to two doses, one dose at 9 and one dose at 15 months of age. Since 1992, the second dose of measles vaccine has been given as measles-mumps-rubella (MMR) vaccine. The most recent effort to eliminate measles was a mass revaccination program, which took effect in 1992; all primary school and junior high school children were given one dose of MMR vaccine regardless of their previous vaccination status, and from 1992 to 1994, every child who had received only one dose of measles vaccine was boosted with one dose of MMR vaccine at primary school entry.

The present seroepidemiological survey was undertaken to evaluate the effectiveness of this mass revaccination program in Taiwan, and to understand the current measles immune status in the general population.

MATERIALS AND METHODS

Study Population

Two batches of serum samples were collected. The first batch consisted of 90 serum samples collected at National Taiwan University Hospital between 1990 and 1992 from children aged 2 years; 42 serum samples were from males and 48 from females. The second batch consisted of 1,281 serum samples collected at National Taiwan University Hospital and Hsinyi District Health Center between 1993 and 1995 from persons aged 2 months to above 30 years. Both institutions are located in Taipei city, the capital of Taiwan. All subjects were apparently healthy and experiencing no acute illness at the time of blood sampling. Oral consent was obtained from every subject or his/her guardian. Serum samples were collected by centrifugation of blood at 1,500 rpm for 5 minutes and then stored at -20°C until tested.

Determination of Antibodies

The serolevel of measles-specific IgG was measured by enzyme-linked immunosorbent assay (ELISA) using a MEASELISA II test kit (Biowhittaker, MD). Standard ELISA procedures were followed. Briefly, the serum samples were added to wells coated with measles virus antigen and incubated for 45 minutes followed by washing to remove unbound antibodies with a buffer. Alkaline phosphatase-conjugated goat antihuman IgG was added to the wells and the reaction mixture was incubated for 45 minutes followed by washing to remove unbound conjugate. The enzyme substrate was then added and incubated for 45 minutes; hydrolyzed enzyme substrate produced a pink color. Spectrophotomet-

ric measurement of the OD₅₅₀ of the wells and linear regression analysis were performed with calibrators and control sera. Levels of anti-measles antibody with a MEASELISA value of ≥ 0.16 were considered positive. Values of ≤ 0.13 were considered negative. The equivocal samples (between 0.14 and 0.15) were repeated and excluded if still equivocal.

RESULTS

The age-specific seropositive rates of measles antibody after the revaccination campaign are shown in Table I and Figure 1. No significant sexual difference was discerned. The measles seropositive rate was lowest among children aged 5–7 months, increased to 85.9% in children aged 12–14 months, and reached the plateau of around 90% in the group aged 2 years. Thereafter, a seropositive rate over 90% was seen in almost all age groups including pregnant women except for the groups aged 4 years and 21–30 years, which dropped slightly.

Among the 90 pre-revaccination program serum samples, 54 (61.4%) were positive for measles antibody. This rate was significantly lower than that (89.2%, 74/83) of the same age group collected after the nationwide MMR revaccination program ($P < 0.05$; chi-square test with Yates' correction).

DISCUSSION

The current measles seroepidemiology in Taiwan after a national revaccination program is described. About half of 2 to 3-month-old babies were seropositive; the figure declined to 36.4% at the age of 5–7 months, presumably reflecting decaying maternally derived measles antibody. An unexpected increase of the seropositive rate to 85.9% in children aged 12–14 months was noted. This observation was attributed to routine measles vaccination at 9 months old in Taiwan. Children in Taiwan are required to receive one dose of MMR at 15 months of age which further stepped up measles seropositivity to 89.2% in children aged 2 years. Thereafter, around 90% of subjects were measles IgG positive.

Measles seropositivity can result from vaccination or from natural infection. The two most recent measles outbreaks occurred in 1985 and in 1988–1989 [Hsu, 1987; Lee et al., 1987; 1992]. There were only two reported cases in the Taipei area during 1992–1994 [Department of Health, 1993, 1994]. As our study subjects younger than 4 years were not exposed to the measles outbreaks, their measles seropositivity must have resulted from vaccination. In 1992, 61.4% of 2-year-old children were seropositive against measles. Without the revaccination program, we reason that in 1994 the measles seropositive rate among children aged 4 years would remain close to 61%. However, this study revealed more than 90% of 4-year-old children were measles IgG positive. The gap must be due to the revaccination program of 1992. Hence, it is concluded that the revaccination program was effective.

This study showed that after 12 months of age, the measles seropositive rate quickly approached 90%. A

TABLE I. Age-Specific Seropositive Rates of Measles Antibody After the Revaccination Campaign in Taiwan

Age	2–3 m		5–7 m		12–14 m		2 y		3 y		4 y	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Positive	20	25	15	21	45	40	49	25	26	17	32	35
Tested	43	38	50	49	54	45	53	30	28	19	36	42
PR(%) ^a	47%	66%	30%	43%	83%	89%	93%	83%	93%	89%	89%	83%
	5 y		6 y–10 y		11–15 y		16–20 y		21–30 y		>30 y	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Positive	43	34	55	53	80	77	55	47	42	66	41	43
Tested	46	35	59	58	87	79	59	50	49	74	47	44
PR(%)	94%	97%	93%	91%	92%	98%	93%	94%	86%	89%	87%	98%

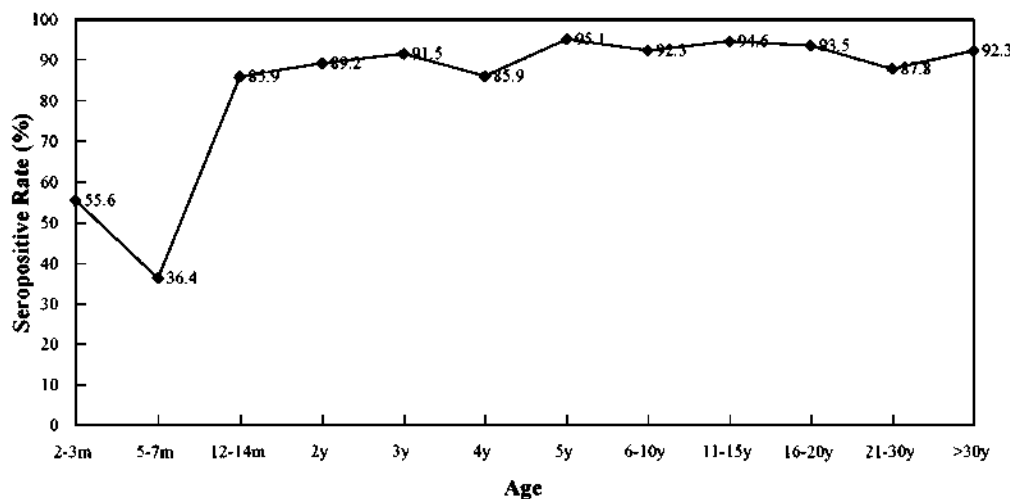
^aPR, positive rate.

Fig. 1. Age-specific seropositive rates of measles antibody after the revaccination campaign in Taiwan.

recent, comparable study done in a southern Taiwan city, Tainan, had similar results [Liu et al., 1996]; the measles seropositive rate in Tainan rose sharply in children after 15 months of age and remained above 90% in children older than 18 months. A theoretical model of the transmission of measles implies herd immunity thresholds in excess of 90% could protect the society from large-scale measles epidemics [Fine, 1993]. However, exceptions to the prediction occurred [Gustafson et al., 1987; Davis et al., 1987]. In the past decade, measles outbreaks were witnessed in some populations with average immunity levels above the proposed 90% herd immunity. It was speculated that a chance aggregation of vaccine failures or a cluster of unvaccinated persons may still lead to epidemics even in a fully immunized population. Some vulnerable age groups with immunity less than 90% were observed in this study, namely, below 1 year, 4 years, and 21–30 years. Therefore, both this study and a study from southern Taiwan [Liu et al., 1996] predict that a large-scale measles outbreak is unlikely to occur, but small outbreaks are still possible.

The seropositive rate in children aged 12–14 months was of interest. Residual maternal antibody can impair the baby's response to measles vaccination [Hasley et al., 1985; Albrecht et al., 1977]. A previous study showed

that the success rate of measles vaccination at 9 months old was 84% and at 12 months old was 88% [Huang et al., 1990]. The present study found that 85.9% (95% confidence interval: 77–92%) of children aged 12–14 months possessed measles antibody. As there was no outbreak after 1990, we assume that all their antibodies were induced by measles vaccination. If the measles vaccination response rate remained unchanged, the vaccination rate would range from 91.6% to over 100% to achieve 85.9% when the vaccine is given at 9 months of age. Even if we assume all the subjects in this age group delayed their measles vaccination until 12 months old, the vaccination rate would range from 87.5% to over 100%. These calculated figures are higher than the official estimates of 79.6%, 86.9%, and 87.9% in 1992, 1993, and 1994, respectively [Department of Health, 1993, 1994, 1995]. Hence, it is possible that response to measles vaccine has improved since we published the previous report [Huang et al., 1990]. This phenomenon is not unexpected as more and more young women derive their measles antibodies through vaccination and were less likely to have natural booster [Wilkins et al., 1972; Yeager et al., 1983; Lennon and Black, 1986; Pabst et al., 1992]. During pregnancy, these women would possess lower levels of measles antibody compared with expectant mothers of previous genera-

tions. The net result is as time goes by, babies will be born with less maternally derived antibody and they will be less likely to suffer from the negative effect of maternal antibody on measles vaccine. Thus, we should witness better measles vaccination effect when given before 1 year of age. The results were in line with the reasoning and this phenomenon deserves further study. Interestingly, this phenomenon was not observed in the study in Tainan [Liu et al., 1996]. They found that 54% of children aged 10–15 months were measles antibody positive. The mothers in Tainan must have possessed higher levels of measles antibody than the mothers in the Taipei area, a reasoning supported by the higher measles seropositive rate (82%) soon after birth in Tainan than the rate (56%) in Taipei.

In summary, this seroepidemiological study revealed that the measles seropositive rate in most age groups has passed the threshold herd immunity of 90% and a large measles epidemic is unlikely in the near future. Increasing immunization levels is the key to eliminate measles. Available strategies include a nationwide re-vaccination campaign, a booster dose of MMR for school-age children, and education about the importance of immunization. For the more urbanized regions, such as Taipei, measles vaccination before 1 year of age is likely to become more effective, and this substantiates the present policy of measles vaccination at 9 months of age.

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